Copy for the Elected Office (EO/US)

PCT/AU99/00597

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

FREEHILLS CARTER SMITH & BEADLE
MLC Centre
Martin Place
Sydney NSW 2000
AUSTRALIE

Date of mailing (day/month/year)
18 December 2000 (18.12.00)

Applicant's or agent's file reference
S2200976

IMPORTANT NOTIFICATION

International application No.
PCT/AU99/00597

International filing date (day/month/year)
23 July 1999 (23.07.99)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☒ the agent ☐ the common representative

Name and Address
GRIFFITH HACK
G.P.O. Box 4164
Sydney, NSW 2001
Australia

State of Nationality

State of Residence

Telephone No.
61 2 9957 5944

Facsimile No.
61 2 9957 6288

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☒ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address
FREEHILLS CARTER SMITH & BEADLE
MLC Centre
Martin Place
Sydney NSW 2000
Australia

State of Nationality

State of Residence

Telephone No.
61 2 9225 5777

Facsimile No.
61 2 9322 4000

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the International Preliminary Examining Authority
☐ the designated Offices concerned
☒ the elected Offices concerned
☒ other: FORMER AGENT

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
A. Karkachi

Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

003729657

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 02 March 2000 (02.03.00)	
International application No. PCT/AU99/00597	**Applicant's or agent's file reference** IHA:FP11264
International filing date (day/month/year) 23 July 1999 (23.07.99)	**Priority date** (day/month/year) 23 July 1998 (23.07.98)
Applicant SMITH, David et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

07 February 2000 (07.02.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Olivia RANAIVOJAONA

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

GRIFFITH HACK
GPO Box 4164
SYDNEY NSW 2001

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *day/month/year*: 28 JUN 2000

Applicant's or agent's file reference: FP11264

IMPORTANT NOTIFICATION

International application No.	International filing date	Priority date
PCT/AU99/00597	23 July 1999	23 July 1998

Applicant: SMITH, David et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translations to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide

Name and mailing address of the IPEA/AU

AUSTRALIAN PATENT OFFICE
PO BOX 200, WODEN ACT 2606, AUSTRALIA
E-mail address: pct@ipaustralia.gov.au
Facsimile No. (02) 6285 3929

Authorized officer

MICHAEL HARDY

Telephone No. (02) 6283 2547

PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Griffith Hack
GPO Box 4164
SYDNEY NSW 2001

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	25 FEBRUARY 2000
Applicant's or agent's file reference FP11264	REPLY DUE within **TWO MONTHS** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/AU 99/00597	23 July 1999	23 July 1998

International Patent Classification (IPC) or both national classification and IPC

Int. Cl.[7] G06F 19/00, 159:00

Applicant

SMITH, David, Dr., et al.

1. This written opinion is the **first** drawn by this International Preliminary Examining Authority.
2. This opinion contains indications relating to the following items:.

I	[X]	Basis of the opinion
II	[ ]	Priority
III	[ ]	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	[ ]	Lack of unity of invention
V	[X]	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	[ ]	Certain documents cited
VII	[ ]	Certain defects in the international application
VIII	[ ]	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4*bis*. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: **23 November 2000**

Name and mailing address of the IPEA/AU

AUSTRALIAN PATENT OFFICE
PO BOX 200, WODEN ACT 2606, AUSTRALIA
E-mail address: pct@ipaustralia.gov.au
Facsimile No. (02) 6285 3929

Authorized Officer

MICHAEL HARDY
Telephone No. (02) 6283 2547

WRITTEN OPINION

International application No.
PCT/AU 99/00597

I. Basis of the opinion

1. With regard to the elements of the international application:*

- [X] the international application as originally filed.
- [ ] the description, pages , as originally filed,
  pages , filed with the demand,
  pages , filed with the letter of .
- [ ] the claims, pages , as originally filed,
  pages , as amended under Article 19,
  pages , filed with the demand,
  pages , filed with the letter of .
- [ ] the drawings, pages , as originally filed,
  pages , filed with the demand,
  pages , filed with the letter of .
- [ ] the sequence listing part of the description:
  pages , as originally filed
  pages , filed with the demand
  pages , filed with the letter of .

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

- [ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- [ ] the language of publication of the international application (under Rule 48.3(b)).
- [ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

- [ ] contained in the international application in printed form.
- [ ] filed together with the international application in computer readable form.
- [ ] furnished subsequently to this Authority in written form.
- [ ] furnished subsequently to this Authority in computer readable form.
- [ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- [ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. [ ] The amendments have resulted in the cancellation of:
   - [ ] the description, pages
   - [ ] the claims, Nos.
   - [ ] the drawings, sheets/fig.

5. [ ] This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	YES
	Claims 1 to 21	NO
Inventive step (IS)	Claims	YES
	Claims 1 to 21	NO
Industrial applicability (IA)	Claims 1 to 21	YES
	Claims	NO

2. Citations and explanations

D1: **Yagyu et al.**, Global Dimensional Complexity of Multichannel EEG in Mild Alzheimer's Disease and Age-Matched Cohorts, *Dementia and Geriatric Cognitive Disorders*, Vol 8, No. 6, 1997, pages 343-347.

D2: **Bastiaanssen et al.**, State-space Analysis of a Myocybernetic Model of the Lower Urinary Tract, *Journal of Theoretical Biology*, Vol 180(3), 7 June 1996, pages 215-227.

D3: Witt, Multichannel Evoked Potentials as Voltage Space Trajectories, *Mathematical Biosciences* Vol 124(2) December 1994, pages 207-224.

D4: Kaplan, Geometrical Techniques for Analyzing ECG Dynamics, *Journal of Electrocardiology* Vol 24 (supplement) 1992, pages 77-82.

D5: **Eisenhammer et al.**, Modeling Experimental Time Series with Ordinary Differential Equations, *Biological Cybernetics*, Vol 65 No. 2, 1991, pages 107-112.

D6: **Park et al.**, Mathematical Modeling of Differentiation in Dictyostelium Discoideum, *Molecular & Cellular Biochemistry*, Vol 8 No 2, 31 August 1975.

All of the above cited documents discuss in one way or another means for representing the time dependent evolution of a biological system as a trajectory in a multi-dimensional state space. Documents D1 to D6 therefor each individually disclose all the essential features of claim 1 at least. It is also clear on the face of each document that computers have been used to collate, analyse and display the data so obtained, and therefor D1 to D6 each individually disclose claims 8, 14, 15 and 21.

D1: (Yagyu et al.) discloses a comparative study of multichannel EEG sequences from three age-matched groups of subjects: mild Alzheimer's disease, mild cognitive impairment and subjective memory complaint. For each subject a sequence of momentary brain field maps was obtained, each brain field map being a K channel eyes-closed EEG of the subject. The sequence of brain field maps thus constitute a trajectory through a K-dimensional state space. The complexity of each trajectory was analysed and a Global Dimensional Complexity (GDC) score for the trajectory was calculated. The variance between GDC scores for the three subject groups was significant suggesting a possible diagnostic tool for distinguishing Alzheimer's disease patients form other forms of cognitive impairment. D1 thus discloses claims 1, 7, 8, 14, 15 and 21.

Continued

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V

D2: (Bastiaanssen et al.) analyses a software model of muscles and neurones of the lower urinary tract. The behaviour of the model is represented as a trajectory in a three dimensional state space of the model (figure 1). Figures 2, 3 and 4 are matrices of calculated curves for one variable as a function of particular states of the remaining variables; ie. they represent surfaces of the trajectory for particular values of the variables representing a predetermined state of the lower urinary tract model. D2 is an example of using a trajectory in an N-dimensional state space to represent the behaviour of a biological system evolving over time. D2 also describes surfaces within the state space representing particular states or conditions of the biological system being analysed. Claims 1 to 21 cannot be inventively distinguished from the disclosure of D2.

D3: (Witt) discusses a method of analysing multichannel brain evoked potentials represented as trajectories in N-dimensional voltage space, analogous to three-channel Lissajous trajectories. Subspaces of the state space are analysed (ie. surfaces normal to the trajectory vector) and abnormal orientations of the subspace are thought to be associated with an underlying structural or functional abnormality of the brain (pages 215 to 217). D3 thus discloses claims 1 to 4, 7 to 12, 14 to 19 and 21.

D4: (Kaplan) discloses a method of representing electrocardiogram signals (ECG) as trajectories in a state space. This technique is useful for detecting and quantifying normal and abnormal dynamics in the heart. Kaplan thus teaches claims 1 to 4, 7 to 12, 14 to 19 and 21.

D5: (Eisenhammer et al.) discusses in general terms the representation of data obtained from experimental time series in the form of a trajectory in a state space and analytical methods associated with this representation. One example included in the paper is that of oscillatory movement of the human hand. D5 thus discloses claims 1 to 4, 7 to 12, 14 to 19 and 21.

D6: (Park et al.) teaches methods of analysing the temporal evolution of a biological system (in particular, the biochemical differentiation of the carbohydrate system in Dictyostelium discoideum) including representing the evolution as a trajectory in an N-dimensional state space. Concepts such as simplifying the description of the system by projecting the trajectory into lower dimensional subspaces are discussed in detail. The use of computers to model and predict the dynamical behaviour of a biological system is also discussed. Claims 1 to 21 cannot be distinguished from the disclosure of D6.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

RECD 04 JUL 2000
WIPO PCT

16

Applicant's or agent's file reference FP11264	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International application No. **PCT/AU99/00597**	International filing date *(day/month/year)* 23 July 1999	Priority Date *(day/month/year)* 23 July 1998

International Patent Classification (IPC) or national classification and IPC

Int. Cl. [7] G06F 19/00, 159:00

Applicant

SMITH, David et al

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets, including this cover sheet.

[X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of **nine (9)** sheet(s).

3. This report contains indications relating to the following items:

I	[X]	Basis of the report
II	[ ]	Priority
III	[ ]	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	[ ]	Lack of unity of invention
V	[X]	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	[ ]	Certain documents cited
VII	[ ]	Certain defects in the international application
VIII	[ ]	Certain observations on the international application

Date of submission of the demand	Date of completion of the report
7 February 2000	26 June 2000
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **MICHAEL HARDY** Telephone No. (02) 6283 2547

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU99/00597

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed.

☒ the description, pages **1, 2, 5 to 10, 12 to 23** as originally filed,
pages , filed with the demand,
pages **3, 4, 4a, 11, 11a** received on **9June 2000** with the letter of **9 June 2000**

☒ the claims, pages , as originally filed,
pages , as amended (together with any statement) under Article 19,
pages , filed with the demand,
pages **24 to 27 (claims 1 to 21),** received on **9 June 2000** with the letter of **9 June 2000**

☒ the drawings, pages **1/4 to 4/4,** as originally filed,
pages , filed with the demand,
pages , received on with the letter of

☐ the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , received on with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, was on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages

☐ the claims, Nos.

☐ the drawings, sheets/fig.

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims **1 to 21**	**YES**
	Claims	**NO**
Inventive step (IS)	Claims **1 to 21**	**YES**
	Claims	**NO**
Industrial applicability (IA)	Claims **1 to 21**	**YES**
	Claims	**NO**

2. Citations and explanations (Rule 70.7)

D1: **Yagyu et al.**, Global Dimensional Complexity of Multichannel EEG in Mild Alzheimer's Disease and Age-Matched Cohorts, *Dementia and Geriatric Cognitive Disorders*, Vol 8, No. 6, 1997, pages 343-347.

D2: **Bastiaanssen et al.**, State-space Analysis of a Myocybernetic Model of the Lower Urinary Tract, *Journal of Theoretical Biology*, Vol 180(3), 7 June 1996, pages 215-227.

D3: **Witt**, Multichannel Evoked Potentials as Voltage Space Trajectories, *Mathematical Biosciences* Vol 124(2) December 1994, pages 207-224.

D4: **Kaplan**, Geometrical Techniques for Analyzing ECG Dynamics, *Journal of Electrocardiology* Vol 24 (supplement) 1992, pages 77-82.

D5: **Eisenhammer et al.**, Modeling Experimental Time Series with Ordinary Differential Equations, *Biological Cybernetics*, Vol 65 No. 2, 1991, pages 107-112.

D6: **Park et al.**, Mathematical Modeling of Differentiation in Dictyostelium Discoideum, *Molecular & Cellular Biochemistry*, Vol 8 No 2, 31 August 1975.

Documents D1 to D6 each disclose methods of representing the evolution of a biological system as a trajectory of the system in an n-dimensional phase or state space. None of the cited documents teaches the formulation of "an n-dimensional surface representing a predetermined state of the biological system within the n-dimensional space" as is defined in the independent claims 1, 8, 14, 15 and 21. This distinction has certain advantages over the prior art methods of representation, particularly in regard to identifying abnormal conditions of the biological system, or for predicting future trends in the evolution of the system. Claims 1 to 21 are therefor novel and involve an inventive step over the cited prior art.

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

PCT/AU 99 / 00597
International Application No.

23 JUL 1999 (23.07.99)
International Filing Date

Australian Patent Office
PCT INTERNATIONAL APPLICATION
Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference (if desired) (12 characters maximum) MHK:IHA:FP11264

Box No. I TITLE OF INVENTION

A Method for Analysis of Biological Systems

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

SMITH, David, Dr.
4 Sakonia Close
Wallsend NSW 2287
Australia

[X] This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(that is, country)* of nationality: Australia

State *(that is, country)* of residence: Australia

This person is applicant for the purposes of: [X] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

SMITH, Roger, Dr.
56 Memorial Drive
Newcastle NSW 2300
Australia

This person is:

[ ] applicant only

[X] applicant and inventor

[ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: Australia

State *(that is, country)* of residence: Australia

This person is applicant for the purposes of: [X] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the Supplemental Box

[ ] Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: [X] agent [ ] common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Griffith Hack
GPO Box 4164
Sydney NSW 2001
AUSTRALIA

Telephone No. 61 2 9957 5944

Facsimile No. 61 2 9957 6288

Teleprinter No.

[ ] Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

- ☒ AP **ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SL Sierra Leone, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ EA **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP **European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ OA **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- ☒ AE United Arab Emirates
- ☒ AL Albania .....
- ☒ AM Armenia .....
- ☒ AT Austria .....
- ☒ AU Australia .....
- ☒ AZ Azerbaijan
- ☒ BA Bosnia and Herzegovina .....
- ☒ BB Barbados
- ☒ BG Bulgaria .....
- ☒ BR Brazil .....
- ☒ BY Belarus .....
- ☒ CA Canada
- ☒ CH and LI Switzerland and Liechtenstein
- ☒ CN China .....
- ☒ CU Cuba .....
- ☒ CZ Czech Republic .....
- ☒ DE Germany .....
- ☒ DK Denmark .....
- ☒ EE Estonia .....
- ☒ ES Spain .....
- ☒ FI Finland .....
- ☒ GB United Kingdom
- ☒ GD Grenada
- ☒ GE Georgia .....
- ☒ GH Ghana .....
- ☒ GM Gambia
- ☒ HR Croatia .....
- ☒ HU Hungary .....
- ☒ ID Indonesia
- ☒ IL Israel .....
- ☒ IN India .....
- ☒ IS Iceland
- ☒ JP Japan .....
- ☒ KE Kenya .....
- ☒ KG Kyrgyzstan .....
- ☒ KP Democratic People's Republic of Korea .....
- ☒ KR Republic of Korea .....
- ☒ KZ Kazakhstan .....
- ☒ LC Saint Lucia
- ☒ LK Sri Lanka
- ☒ LR Liberia
- ☒ LS Lesotho .....
- ☒ LT Lithuania
- ☒ LU Luxembourg
- ☒ LV Latvia
- ☒ MD Republic of Moldova .....
- ☒ MG Madagascar .....
- ☒ MK The former Yugoslav Republic of Macedonia .....
- ☒ MN Mongolia
- ☒ MW Malawi .....
- ☒ MX Mexico .....
- ☒ NO Norway
- ☒ NZ New Zealand .....
- ☒ PL Poland .....
- ☒ PT Portugal .....
- ☒ RO Romania
- ☒ RU Russian Federation .....
- ☒ SD Sudan
- ☒ SE Sweden
- ☒ SG Singapore
- ☒ SI Slovenia .....
- ☒ SK Slovakia .....
- ☒ SL Sierra Leone .....
- ☒ TJ Tajikistan .....
- ☒ TM Turkmenistan .....
- ☒ TR Turkey .....
- ☒ TT Trinidad and Tobago .....
- ☒ UA Ukraine .....
- ☒ UG Uganda .....
- ☒ US United States of America .....
- ☒ UZ Uzbekistan .....
- ☒ VN Viet Nam .....
- ☒ YU Yugoslavia .....
- ☒ ZA South Africa .....
- ☒ ZW Zimbabwe .....

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:

- ☐ .....
- ☐ .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 23 July 1999	PP6634	Australia		
item (2)				
Item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s):

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):*

ISA /

Request to use results of earlier search; reference to that search *(If an earlier search has been carried out by or requested from the International Searching Authority):*

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following number of sheets:

request	:	3
description (excluding sequence listing part)	:	23
claims	:	4
abstract	:	1
drawings	:	4
sequence listing part of description	:	
Total number of sheets	:	35

This international application is accompanied by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other *(specify)*:

Figure of the drawings which should accompany the abstract: 1

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Robert Griffith

Registered Patent Attorney
for and on behalf of
Griffith Hack

For receiving Office use only

1. Date of actual receipt of the purported international application: 23 JUL 1999 (23.07.99)
2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA /
6. ☐ Transmittal of search copy delayed until search fee is paid.

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Date of receipt of the record copy by the International Bureau:

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference FP11264	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International application No. PCT/AU99/00597	International filing date *(day/month/year)* 23 July 1999	Priority Date *(day/month/year)* 23 July 1998

International Patent Classification (IPC) or national classification and IPC

Int. Cl. [7] G06F 19/00, 159:00

Applicant

SMITH, David et al

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets, including this cover sheet.

[X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of nine (9) sheet(s).

3. This report contains indications relating to the following items:

I	[X]	Basis of the report
II	[ ]	Priority
III	[ ]	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	[ ]	Lack of unity of invention
V	[X]	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	[ ]	Certain documents cited
VII	[ ]	Certain defects in the international application
VIII	[ ]	Certain observations on the international application

Date of submission of the demand	Date of completion of the report
7 February 2000	26 June 2000
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer MICHAEL HARDY Telephone No. (02) 6283 2547

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU99/00597

I Basis of the report

1. With regard to the elements of the international application:*

- [ ] the international application as originally filed.
- [X] the description, pages 1, 2, 5 to 10, 12 to 23 as originally filed,
  pages , filed with the demand,
  pages 3, 4, 4a, 11, 11a received on 9June 2000 with the letter of 9 June 2000
- [X] the claims, pages , as originally filed,
  pages , as amended (together with any statement) under Article 19,
  pages , filed with the demand,
  pages 24 to 27 (claims 1 to 21), received on 9 June 2000 with the letter of 9 June 2000
- [X] the drawings, pages 1/4 to 4/4, as originally filed,
  pages , filed with the demand,
  pages , received on with the letter of
- [ ] the sequence listing part of the description:
  pages , as originally filed
  pages , filed with the demand
  pages , received on with the letter of

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, ~~unless otherwise indicated under this item.~~
These elements were available or furnished to this Authority in the following language which is:

- [ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- [ ] the language of publication of the international application (under Rule 48.3(b)).
- [ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, was on the basis of the sequence listing:

- [ ] contained in the international application in written form.
- [ ] filed together with the international application in computer readable form.
- [ ] furnished subsequently to this Authority in written form.
- [ ] furnished subsequently to this Authority in computer readable form.
- [ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- [ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. [ ] The amendments have resulted in the cancellation of:
   - [ ] the description, pages:
   - [ ] the claims, Nos.
   - [ ] the drawings, sheets/fig.

5. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU99/00597

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1 to 21	YES
	Claims	NO
Inventive step (IS)	Claims 1 to 21	YES
	Claims	NO
Industrial applicability (IA)	Claims 1 to 21	YES
	Claims	NO

2. Citations and explanations (Rule 70.7)

D1: Yagyu et al., Global Dimensional Complexity of Multichannel EEG in Mild Alzheimer's Disease and Age-Matched Cohorts, *Dementia and Geriatric Cognitive Disorders*, Vol 8, No. 6, 1997, pages 343-347.

D2: Bastiaanssen et al., State-space Analysis of a Myocybernetic Model of the Lower Urinary Tract, *Journal of Theoretical Biology*, Vol 180(3), 7 June 1996, pages 215-227.

D3: Witt, Multichannel Evoked Potentials as Voltage Space Trajectories, *Mathematical Biosciences* Vol 124(2) December 1994, pages 207-224.

D4: Kaplan, Geometrical Techniques for Analyzing ECG Dynamics, *Journal of Electrocardiology* Vol 24 (supplement) 1992, pages 77-82.

D5: Eisenhammer et al., Modeling Experimental Time Series with Ordinary Differential Equations, *Biological Cybernetics*, Vol 65 No. 2, 1991, pages 107-112.

D6: Park et al., Mathematical Modeling of Differentiation in Dictyostelium Discoideum, *Molecular & Cellular Biochemistry*, Vol 8 No 2, 31 August 1975.

Documents D1 to D6 each disclose methods of representing the evolution of a biological system as a trajectory of the system in an n-dimensional phase or state space. None of the cited documents teaches the formulation of "an n-dimensional surface representing a predetermined state of the biological system within the n-dimensional space" as is defined in the independent claims 1, 8, 14, 15 and 21. This distinction has certain advantages over the prior art methods of representation, particularly in regard to identifying abnormal conditions of the biological system, or for predicting future trends in the evolution of the system. Claims 1 to 21 are therefor novel and involve an inventive step over the cited prior art.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 99/00597

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: G06F 19/00, 159:00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC G06F 159:00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
MEDLINE on Internet
"trajectory" or "phase space" or "state space"

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Yagyu et al., Global Dimensional Complexity of Multichannel EEG in Mild Alzheimer's Disease and Age-Matched Cohorts, Dementia and Geriatric Cognitive Disorders, Vol 8, No. 6, 1997, pages 343-347. See abstract	1, 7, 8, 14, 15, & 21
X	Bastiaanssen et al., State-space Analysis of a Myocybernetic Model of the Lower Urinary Tract, Journal of Theoretical Biology, Vol 180(3), 7 June 1996, pages 215-227. See whole document.	1 to 21
X	Witt, Multichannel Evoked Potentials as Voltage Space Trajectories, Mathematical Biosciences Vol 124(2) December 1994, pages 207-224. See whole document.	1 to 4, 7 to 12, 14 to 19 & 21

[X] Further documents are listed in the continuation of Box C

[ ] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 August 1999	07 SEP 1999
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No.: (02) 6285 3929	Authorized officer Michael Hardy Telephone No.: (02) 6283 2547

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 99/00597

C (Continuation). **DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Kaplan, Geometrical Techniques for Analyzing ECG Dynamics, Journal of Electrocardiology Vol 24 (supplement) 1992, pages 77-82. See whole document.	1 to 4, 7 to 12, 14 to 19 &21
X	Eisenhammer et al., Modeling Experimental Time Series with Ordinary Differential Equations, Biological Cybernetics, Vol 65 No. 2, 1991, pages 107-112. See whole document.	1 to 4, 7 to 12, 14 to 19 & 21
X	Park et al., Mathematical Modeling of Differentiation in Dictyostelium Discoideum, Molecular & Cellular Biochemistry, Vol 8 No 2, 31 August 1975. See whole document.	1 to 21

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The Commissioner of Patents

PCT Unit

9 June 2000

Sir

IN THE MATTER OF International Patent Application No. PCT/AU99/00597
in the name of DR ROGER SMITH and DR DAVID SMITH
Entitled METHOD FOR ANALYSIS OF BIOLOGICAL SYSTEMS
Our Ref: MHK:IHA:FP11264

Letter accompanying Article 34 amendments

1.	Pages 3, 4	Replace pages 3, 4 presently on file with new pages 3, 4, 4a submitted herewith.
2.	Page 11	Replace page 11 presently on file with new pages 11, 11a submitted herewith.
3.	Claim pages 24 – 27	Replace claim pages 24 – 27 presently on file with new claim pages 24 – 27 submitted herewith.

We enclose annotated pages indicating the location of the Article 34 amendments on the replacement pages.

Yours faithfully
GRIFFITH HACK

Dr Michael Koch

GRIFFITH HACK
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The Commissioner of Patents

PCT Unit

9 June 2000

IN THE MATTER OF International Patent Application No. PCT/AU99/00597
in the name of DR ROGER SMITH and DR DAVID SMITH
Entitled METHOD FOR ANALYSIS OF BIOLOGICAL SYSTEMS
Our Ref: MHK:IHA:FP11264

Sir

In response to the Written Opinion issued on the above listed patent application, we have amended claims 1, 8, and 15 to incorporate features originally claimed in claims 2, 9, 16, respectively.

As a result, all of the independent claims of the present application are now limited to the utilisation of sets of predetermined values of variables to formulate an n-dimensional surface representing a predetermined state of the biological system under investigation within the n-dimensional space.

We respectfully submit that none of the prior art documents cited discloses the utilisation of such a "limit-state" surface within an n-dimensional space as a visual representation of a potential target towards which a trajectory progresses.

Turning initially to document D2 (Bastiaanssen et al), we respectfully disagree with the Examiner's opinion that "Figures 2, 3 and 4 are matrices of calculated curves for one variable as a function of particular states of the remaining variables; i.e. they represent surfaces of the trajectory for particular values of the variables representing a predetermined state of the lower urinary tract model."

We respectfully submit that what is disclosed in D2, is a representation of a fourth dimension (i.e. the rate of change of bladder volume) using a matrix of two-dimensional graphs. By this method, Bastiaanssen effectively achieves a representation of the whole solution space for the four parameters in his mathematical model. Clearly, the representation of a whole solution space is in no way related to the formulation of an n-dimensional surface representing a predetermined state of the biological system under investigation.

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The Commissioner of Patents

PCT Unit

9 June 2000

Sir

IN THE MATTER OF International Patent Application No. PCT/AU99/00597
in the name of DR ROGER SMITH and DR DAVID SMITH
Entitled METHOD FOR ANALYSIS OF BIOLOGICAL SYSTEMS
Our Ref: MHK:IHA:FP11264

In response to the Written Opinion dated 25 February 2000, we submit the following documents:

- Written response
- Article 34 amendments
- Letter accompanying Article 34 amendments, including 7 annotated pages indicating the location of amendments on the replacement pages.

Yours faithfully
GRIFFITH HACK

Dr Michael Koch

Indeed, the inherent differences between the analysis disclosed in D2 and the method of the present application may become more clear by highlighting that the method of the present invention may be utilised to provide a more comprehensible analysis and representation of the information conveyed by the Bastiaanssen model.

In the Bastiaanssen model, a surface representing a predetermined state of the system could for example be a surface of constant rates of change of bladder volume. If a certain rate of change of bladder volume would for example be unsatisfactory, the movement of a patient's trajectory towards the before mentioned surface of the present invention would convey all relevant information that is immediately clinically useful, which lies at the heart of the present invention.

Not having got the benefit of the present invention, Bastiaanssen goes on in Figure 5 of D2 to try and extract some clinically useful information from his mathematical model. In Figure 5, Bastiaanssen presents a division of the matrix of curves shown in Figures 2, 3 and 4. The lines dividing this area into the regions labelled I to IX in Figure 5 do again clearly not represent surfaces either. Bastiaanssen suggests the regions shown in Figure 5 represent "different patterns of behaviour which can be recognised." Feeling this explanation is inadequate, Bastiaanssen goes on to say "more strictly spoken within each area the state trajectories are topologically equivalent: by an invertible mapping the trajectories within one cell of the matrix M can be transformed to the trajectories in another cell within the same area."

Firstly, we respectfully submit that this explanation of Figure 5 is also unsatisfactory. This is because non-invertible mappings between one cell and another in the same area are shown in Figure 2 (e.g. cell row 1, col. 1 with cell row 1, col. 3 in Figure 2 is non-invertible, at least at the level of resolution offered by the graphs shown). Secondly, notwithstanding the inadequate explanation of what information may or may not be extracted from Figure 5, it is clear that Figure 5 does not represent surfaces formulated utilising sets of predetermined values of the variables, the surface thus representing a predetermined state of the biological system under investigation.

In summary, Bastiaanssen et al attempt in D2 to represent the "whole solution" in the chosen four-dimensional state space. In their attempt, they try to represent the whole solution along selected lines in the four-dimensional state space, which we respectfully submit quickly becomes almost incomprehensible. We therefore submit that the new independent claims of the present invention are novel and do involve an inventive step when compared with the disclosure in D2.

Turning next to D3 (Witt), in that document scalp potentials from n-electrodes are analysed. While such a system could be represented in a n-dimensional space, Witt

choses to represent them in lower dimensional sub-spaces. Tensor algebra is used to compare data collected from different montages (i.e. scalp locations for electrodes). Tensor algebra can be used because dipole theory is linear, which means that one can simply sum the potentials from various dipole sources.

Importantly, the Examiner seems to have equated a sub-space of the state space as the "surface" referred to in the present invention. We respectfully submit that this is incorrect. As defined in for example new claim 1, the surface of the present invention is a surface formulated utilising a set of predetermined values of the variables and representing a predetermined state of the biological system within the n-dimensional space. This is clearly in contrast to the concept of utilising a reduced dimension analysis (i.e. a sub-space analysis).

Accordingly, we respectfully submit that D3 also fails to disclose utilising a surface representing a predetermined state of the biological system in an n-dimensional space. The differences between D3 and the present invention are also evident by the fact that nowhere in D3 is it attempted to graphically represent the analysis, which indeed is one of the main advantages that can be offered by the present invention.

In D4 (Kaplan), an "embedding transform" is utilised to analyse a signal over time. This transform converts the signal over time into a trajectory in an n-dimensional space. Various statistics aimed at identifying clinically useful abnormalities are used to describe the trajectories. However, there is no discussion or disclosure whatsoever of surfaces representing predetermined states of the biological system under investigation. We therefore respectfully submit that the new independent claims of the present invention are patentably distinguishable from the disclosure in D4.

D5 (Eisenhammer et al) is aimed at fitting a model to data collected over time. Whilst this document utilises an approach which involves state-spaces, there is no disclosure whatsoever in that document of a surface representing a predetermined state of the biological system under investigation within the state-spaces. Accordingly, we respectfully submit that the present invention is patentably distinguishable from the disclosure in D5.

Turning finally to D6 (Park et al) the Examiner states that "concepts such as simplifying the description of the system by projecting the trajectory into lower dimensional sub-spaces are discussed in detail". Referring back to the preceding discussion of the various prior art documents, we respectfully submit that this statement seems to illustrate the misunderstanding of what is referred to in the present specification as "limit-state surfaces".

9 June 2000

As defined in for example new claim 1, the present invention utilises sets of predetermined values of the variables to formulate an n-dimensional surface representing a predetermined state of the biological system within the n-dimensional space. This concept has to be contrasted with the mere "simplification" of projecting a n-dimensional state space into a lower dimensional sub-space. Such simplifications are aimed at trying to simplify a representation of the whole solution space for a particular system. The sub-space itself is not representative of a predetermined state of the biological system at all.

For completeness, we also note that for example in Figure 3 of D6, equal time surfaces/planes, are depicted. Such equal time surfaces/planes also have to be contrasted with the surfaces as defined in for example new claim 1 of the present application, i.e. time is not a predetermined state of the biological system under investigation. Park et al merely utilises equal time surfaces/planes as "reference points" for comparing trajectory bundles. Clearly, isochronal analysis of trajectories is inherently different from evaluating the evolution of the biological system based on trajectories and an n-dimensional surface representing a predetermined state of the biological system within the n-dimensional space, that surface being formulated from sets of predetermined values of the variables within the n-dimensional space.

We also note that having limited the independent claims of the present application to the utilisation of surfaces representing a predetermined state of the biological system under investigation, those claims are now also patentably distinguishable from the disclosure in D1 (Yagyu et al), in which there is no mention at all of a limit-state surface with a physiological interpretation.

We have further amended the preamble of the specification to conform with the amended claims and have added new claims 6, 13, and 20 directed to a feature of the preferred embodiment described in the present specification.

Reconsideration of the objections raised in the Written Opinion is respectfully requested.

Yours faithfully
GRIFFITH HACK

Dr Michael Koch

M·H

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : G06F 19/00 // 159:00

A1

(11) International Publication Number: WO 00/05671

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(22) International Filing Date: 23 July 1999 (23.07.99)

(30) Priority Data:
PP 6634 23 July 1998 (23.07.98) AU

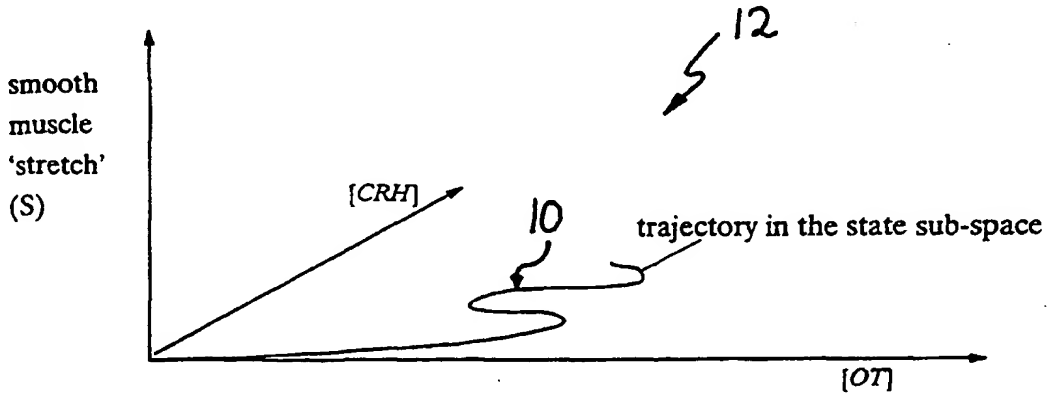
(71)(72) Applicants and Inventors: SMITH, David [AU/AU]; 4 Sakonia Close, Wallsend, NSW 2287 (AU). SMITH, Roger [AU/AU]; 56 Memorial Drive, Newcastle, NSW 2300 (AU).

(74) Agent: GRIFFITH HACK; G.P.O. Box 4164, Sydney, NSW 2001 (AU).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: A METHOD FOR ANALYSIS OF BIOLOGICAL SYSTEMS



(57) Abstract

A method of analysing an evolution of a biological system comprising the steps of determining a series of variables upon which a state of the biological system depends, mapping the variables to an n–dimensional space, and wherein the evolution of the biological system is monitored utilising a trajectory formed from sets of the variables which define the states of the biological system at different times, thereby using time as a parameter in the n–dimensional space in a manner such that every point on the trajectory corresponds to at least one value of time.

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A METHOD FOR ANALYSIS OF BIOLOGICAL SYSTEMS

Field of the Invention

The present invention relates to the organisation and interpretation of data relating to biological systems. The invention will be described hereinafter in the context of medical research/clinical management of patients, i.e. using medical terminology, but it will be understood that the present invention does have broader applications to biological systems in general.

Background of the Invention

In medical research and monitoring of patient behaviour it is currently the usual approach to "pool" data, i.e. to base an analysis on trends derived by averaging particular data obtained from a large number of patients in a suitable way. It is further common to limit an evaluation of a patient's behaviour to one variable at a time, i.e. the development of a particular variable is followed over time and, for example, charts illustrating the development are used to assist the practitioner in his assessment of the patient behaviour. This has several disadvantages.

For example, the reliance upon averaged data in evaluating the patient behaviour somewhat limits the spectrum of the assessment made as extreme values on opposite sides of the average are effectively cancelled out of consideration in the assessment. Another disadvantage is that this "one variable at a time" approach makes it more difficult for the practitioner to remain alert to various other variables which could form a complex interrelationship with the particular variable when evaluating the patient behaviour. This is not to say that practitioners in general are not alert to this problem, but the likelihood of not taking into consideration all necessary variables is increased.

In current medical practice one variable at a time

(e.g. temperature) is plotted against time. Time appears as an independent variable typically along the X-axis and e.g. temperature along the Y-axis. Many such separate two-dimensional graphs are used to plot various variables such as blood pressure against time, urinary volume against time, heart rate against time etc., each variable being depicted on a separate graph. Up to now, the use of time as the independent variable plotted along one axis of the graph somewhat dictates the preferred use of a multiplicity of two-dimensional graphs when managing medical data.

In contrast, it is known that physicists employ a set of variables to describe the behaviour of a particular system in a three-dimensional space. A well-known example that is a paradigm for the scientific method is provided by the behaviour of an ideal gas. In this case the variables are pressure, volume and temperature and together they define a three-dimensional space. Those variables are related by the well known "equation of state for an ideal gas"

$$P V = n R T.$$

In this equation n is the number of moles of gas present in the system and R is the universal gas constant. This equation may be represented as a surface in the three-dimensional space and represents each "allowed" state of an ideal gas in those three dimensions.

Summary of the Invention

At least preferred embodiments of the present invention can enhance the management and interpretation of data relating to a biological system to thereby improve e.g. the assessment capabilities of a non-specialist doctor.

In accordance with a first aspect of the present invention there is provided a method of analysing an evolution of a biological system comprising the steps of determining a series of variables upon which a state of the

biological system depends, mapping the variables to an n-dimensional space, wherein the evolution of the biological system is monitored utilising a trajectory formed from sets of the variables which define the states of the biological system at different times, thereby using time as a parameter in the n-dimensional space in a manner such that every point on the trajectory corresponds to at least one value of time.

In that way, time is used as a "hidden" variable to analyse the evolution of the biological system, which can facilitate an improved method of analysing the evolution of the biological system in which the interrelationship between the variables upon which the state of the biological system depends can become more apparent.

In one embodiment, the method further comprises the step of evaluating the evolution of the biological system utilising sets of predetermined values of the variables to formulate an n-dimensional surface representing a predetermined state of the biological system within the n-dimensional space.

Preferably, n is an integer greater than 2.

In one embodiment, the step of evaluating the evolution of the biological system comprises predicting a progression of the trajectory.

Preferably, the prediction of the progression of the trajectory is based on the previous development of the trajectory within the n-dimensional space.

In another embodiment, the prediction of the progression of the trajectory is based on other trajectories determined in the n-dimensional space.

In accordance with a second aspect of the present invention there is provided a method of representing a predetermined state of a biological system comprising the steps of determining a series of variables upon which the predetermined state of the biological system depends,

mapping the variables to an n-dimensional space and utilising sets of predetermined values of the variables to formulate an n-dimensional surface describing the predetermined state within the n-dimensional space.

In accordance with a third aspect of the present invention there is provided a computer arranged to analyse an evolution of a biological system based on a series of variables upon which a state of the biological system depends, the computer being arranged to map the variables to an n-dimensional space, and to monitor the evolution of the biological system based on a trajectory formed from sets of the variables which define the states of the biological system at different times.

In accordance with a fourth aspect of the present invention there is provided a computer arranged to represent a predetermined state of a biological system based on a series of variables upon which the predetermined state of the biological system depends, the computer being arranged to map the variables to an n-dimensional space and to formulate an n-dimensional surface describing the predetermined state within the n-dimensional space, based on sets of predetermined values of the variables.

In accordance with a fifth aspect of the present invention there is provided a computer readable storage medium comprising instructions to control a computer to analyse an evolution of a biological system based on series of variables upon which a state of the biological system depends, the instructions comprising instruction to control the computer to map the variables to an n-dimensional space; and monitor the evolution of the biological system based on a trajectory formed from sets of the variables which define the states of the biological system at different times.

In accordance with a sixth aspect of the present invention there is provided a computer readable storage

medium comprising instructions to control a computer to represent a predetermined state of a biological system based on a series of variables upon which the predetermined state of the biological system depends, the instructions comprising instructions to control the computer to map the variables to an n-dimensional space; and formulate an n-dimensional surface describing the predetermined state within the n-dimensional space, based on sets of predetermined values of the variables.

The present invention may be applicable, but is not restricted to use in a clinical context, in medical research and in medical training. The medical training can comprise both medical training of persons in the medical profession and training/developing a better patient's understanding.

Embodiments of the invention may play an important role in assisting patients to understand, firstly, what is wrong. For example, they may be moving along a trajectory that is likely to lead to a disease state, such as cardiovascular disease. Secondly, they may assist patients to then appreciate what has to be done to ensure a healthy state is maintained or regained. This could be a valuable tool facilitating doctor-patient relationships and improving patient compliance with the proposed treatment regime.

Embodiments of the invention may be employed as valuable educative tool when training health professionals. The concept of a state-space, current location in the state-space and proximity to various limit-states is a valuable method for representing normality and disease and this may facilitate the education of medical professionals. The conceptual framework of the invention can be presented graphically. Details of how this can be done can be found in the description of preferred embodiments of the invention. All disease states may be viewed as a movement

toward some particular limit-state surface in some state-space. The signs and symptoms of disease may be viewed as particular locations in a state-space in relation to suitably chosen limit-state surfaces.

An important part of the medical interview is the patient history. In the context of the invention as described here, this history may be interpreted as the patient's perception of their proximity to various limit-state surfaces. This information may be incorporated into embodiments of the invention in a semi-quantitative way (ie. by employing a magnitude on some appropriate scale and limit-state surfaces at appropriate locations in the state-space).

With the assistance of a suitable computer program, the systematic evaluation of various treatment scenarios could be examined in a clinical environment by the treating physician but may also be used in controlled learning environment using the model, in much the same way as pilots are trained using a flight simulator by an instructor. It will be understood by a person skilled in the art that known techniques such as the use of neural networks may be utilised in improving the reliability of simulations.

The invention is also potentially useful in assessing the cost of various treatment alternatives if used in conjunction with a suitable cost database. The model may be a very valuable tool for the allocation of scarce resources by medical management.

The mathematical model used in embodiments of the invention may be 'customised' by experts in the field, reflecting their particular understanding of a subject.

In some cases, previous medical conditions may have lead to realisation of a specific condition (eg. a previous pregnancy, or previous hospitalisation for asthma treatment). This patient specific information may also be incorporated in the model to improve the predictive

capability of the model for that particular patient. Hence, a valuable component of a patients' medical record may be an interpretation of their medical history in terms of the mathematical model described here.

Brief Description of the Drawings

The invention may be more fully understood from the description of preferred forms given below with reference to the accompanying drawings, by way of example only.

In the drawings,

Figure 1 illustrates a state subspace with a trajectory of a patient behaviour in accordance with an embodiment of the present invention.

Figure 2 illustrates another state subspace with trajectory of a patient behaviour in that state subspace.

Figure 3 illustrates the state subspace of Figure 1 with a trial limit-state function describing the occurrence of an event in that state subspace.

Figure 4 illustrates the state subspace of Figure 3 with the trajectory of the patient behaviour of Figure 1.

Figure 5 illustrates trajectories of patient behaviours intersecting multiple event function surfaces in another state subspace.

Figure 6 is a diagram illustrating dependent and independent variables for use in a method in accordance with an embodiment of the present invention.

Description of a Preferred Embodiment

The embodiments of the invention will be described by way of reference to a number of initial examples. However, the scope of the present invention is not limited to these examples. To further illustrate the broader application of the invention, in the following a particular terminology is introduced in which terms are defined in a conceptional sense and then particular examples are given in which the conceptional terms are correlated with specific systems.

The conceptional basis for the invention is the

analysis of a biological system, for example the physiological states in humans, in a multi-dimensional state-space. The dimensions of the state space are correlated with parameters/variables which influence the biological system, i.e. which influence the state of the biological system in respect of the state-space. The behaviour of the biological system can thus be described as the evolution of the state of the system within the state-space over time, i.e. a trajectory of the biological system is monitored and from it the current state of the system can be known. Importantly, provided the state space is chosen correctly, certain states of the biological system within the state-space will be attributable to certain biological events, i.e. the biological state of the system has reached a particular limit-state. Particular examples for limit-states are given below. Generally speaking a limit state is the realisation of a biologically or medically defined state of the system, both normal and abnormal states. As various combinations of different parameters can lead to the realisation of a particular limit-state, the limit-state can be described as a function within the state-space. The relative positioning of the trajectory of a biological system and a limit-state surface within the state-space can form the basis for the development of a systematic method for both differential diagnosis and for patient management. The use of the method for differential diagnosis may form the basis of information structuring in an `expert system' for the purpose of medical differential diagnosis.

The state-space variables may be normalised (non-dimensionalised) by various methods, each method of normalisation resulting in a different depiction of the trajectories and limit surfaces in the normalised state-space.

One normalisation method can reduce a trajectory to a

point in the normalised state-space. If the trajectory that is reduced to a point in the normalised state-space is the mean (or median or mode) trajectory, then trajectories in the normalised state-space will represent departures from this mean (or median or mode) trajectory.

In the following, examples of preferred embodiments of the invention will be described with reference to the physiological states in humans.

Example I: ANALYSIS OF PHYSIOLOGY OF PREGNANCY

A first example relates to the analysis of pregnancy in women. Pregnancy is distinguished by one very obvious event, giving birth. It is practice to regularly monitor women over the course of the pregnancy, thereby facilitating the monitoring of several parameters during that period.

A careful consideration leads to the initial proposal of the following 'simple' state-space for the assessment of pregnancy. The state-space variables chosen for plotting the trajectories are corticotrophin-releasing-hormone concentration (CRH), oxytocin concentration (OT), progesterone concentration (P), oestrodiol concentration (E), cortisol concentration (C), cervical stiffness (CS) and stretch of the smooth muscle fibres within the uterus (S). S may be a dependent variable from independent variables which could include such quantities as volume of the amniotic fluid and fetal mass. CRH may be a dependent variable from independent variables which could include such quantities as placental mass, maternal blood volume and concentration of maternal CRH binding protein. Other independent variables may also be specified in turn for each of the remaining five state variables.

There may be other known state-variables (eg. relaxin, prostaglandins) or as yet unknown state-variables of importance. It is further observed that failure of the model to achieve the desired reliability could suggest the

presence of additional, as yet unknown factors.

The limit-states that may be of interest for the analysis of pregnancy include 'uterine contractions leading to birth', 'cervical competence' and 'fetal lung maturation'. Only 'uterine contractions leading to birth' will be pursued here as an example. All the state-variables except CS will be employed as state-variables for the analysis of this limit-state.

There are six state variables employed here in the consideration of the 'uterine contractions leading to birth' limit state analysis. Those may be grouped into two state-subspaces, with each state-subspace involving three state-variables (see Figures 1 and 2).

A first trajectory 10 in a first state-subspace 12 is sketched in Figure 1 and a second trajectory 14 in state-subspace 16 is sketched in Figure 2. While the grouping of state-variables may be arbitrary, there may be reasons for choosing one grouping of variables over another. For example, state-variables may be grouped according to clinical importance.

It is seen that the first trajectory 10 in the first state-subspace 12 (Figure 1) oscillates throughout pregnancy due to diurnal fluctuations in the concentration of oxytocin. There may be normal and or abnormal (ie. pathologic) trajectories in this state-subspace. Normal and abnormal behaviours along the CRH axis leading to pre-term, term and post-term parturition have already been identified by the research investigations of Mark McLean, Andrew Bisets, Joanne Davies, Russel Woods, Philip Lowry and Roger Smith (May , 1995), `A placental clock controlling the length of human pregnancy', Nature Medicine, Vol. 1 No. 5 p. 460-463)

It is seen that the second trajectory 14 in Figure 2 also oscillates late in pregnancy due to diurnal fluctuations in the concentration of E and P. (It is noted

here that the E/P ratio may be a more appropriate state-subspace variable, rather than E and P separately). Once again, there may be normal and/or abnormal (ie. pathologic) trajectories in this state-subspace.

The limit-state surface (not shown) in both state-subspaces may evolve (change position) over time. This is due to the fact that the limit-state surface is dependent on variables which are themselves time dependent. A third limit-state surface 20 in one state-subspace 21 (CRH, OT and S), at one particular time, is shown in Figure 3.

It is well known that the processes leading to pregnancy contain redundancies. By this it is meant that some state-variables may not be essential for a normal birth. In other words, a redundant state-variable may be important when present, yet non-essential to a normal birth. It is noted that the described redundancy of state-variables observed during pregnancy is made immediately visually clear by the ellipsoidal shaped limit-state surface proposed here. For example, if CRH is absent (or present in abnormal very low concentrations), then the state-subspace in Figure 3 is reduced to two dimensions, and a women's trajectory in the state-subspace will be confined to a 'plane' in the state-subspace. It is immediately visually apparent that the trajectory confined to this plane can still intersect the limit-state surface. This intersection of trajectory and limit-state surface indicates that progression to birth is still possible.

To better visually comprehend the trajectories of pregnant women in the state-space, it may be advantageous to have the two state-subspaces depicted simultaneously on a computer screen. Time could also be indicated along each trajectory by 'tick' marks. Speed along the trajectory may be indicated by a line of varying thickness, or colour. It is noted in passing that the time lapsed since conception

can be accurately measured using ultra-sonic techniques.

It is probable that the limit-state surface in each state-subspace expands (moves away from the origin) early in pregnancy (due to it being dependent on state variables), and may contract and then oscillate later in pregnancy, thereby precipitating parturition. The oscillation of the trajectory and the limit-state subspace surface is believed to be 'phase locked' (ie. the trajectory in a state-subspace moves away from the origin at the same time as the limit-state surface moves toward the origin). This simple observation, easily visually comprehended using the methods described here, may explain why the initiation of births occur during the night due to a periodical contraction of the limit-state surface during night time.

Now that the limit-state surface is known to be important, the 'shape' of the state surface in a state-subspace may be actively 'probed' by selected tracking of individual women throughout pregnancy. As this data becomes available, it is expected that the trial limit state surface 20 shown in Figure 3 will be modified. This procedure will define normal and abnormal trajectories in the state-space, as well as the shape of the limit-state surface. This empirical approach to define the limit-state surface and trajectories in the state-space may be supplemented when possible by detailed physiological and biochemical models. This method of investigating pregnancy is an example of how the mathematical method described here can be utilised in medical research.

The onset of uterine contractions leading to birth occurs when the trajectory 22 in the 'state-space' 21 intersects the limit-state surface 20. This is shown in the Figure 4. It is clearly advantageous for defining the limit-state surface, to monitor the trajectory accurately close to the time of birth, and preferably obtain a point

in the state-space at the time of birth (ie. on the limit-state surface). However, if this is not possible, it is believed that it may be possible to reliably extrapolate the trajectory in the state-space to the time of birth, given adequate previous knowledge of the trajectory in the state-space and knowledge of the underlying physiological and biochemical processes.

Example II: PREDICTIVE ANALYSIS

The embodiment described above has been described in a deterministic format. However, a statistical analysis of the current location in a state-subspace in relation to the limit-state surface can be easily incorporated in another embodiment. This could be implemented in various ways, a Monte-Carlo simulation being one of the most general method applicable. This embodiment could then be employed to make predictions of the type 'there is a 90% chance that a pre-term delivery will occur'.

It is noted that the effect of a proposed course of medical intervention could be quantitatively assessed by the embodiment described. For example, the likely effect of intervention by a clinician using a CRH antagonist could be shown in the state-space. As there may be several ways of achieving the desired outcome (ie. realisation of the limit state event, or moving away from the limit-state event), alternative treatment methods could be assessed before they are implemented by a clinician. The distance between the current state and the limit-state surface, in conjunction with probability density functions, will give a quantitative measure of likelihood of success or otherwise of the proposed intervention.

It is noted that the distance of interest may not be the 'shortest distance' between the current position in the state-space and the limit-state surface, but could depend on an individual's trajectory in the state-space. If the trajectory is well-defined (ie. both direction and speed is

known, or can be estimated), it may be possible to reliably extrapolate from the current position in the state-spate to some future position in the state-space. If the speed along the trajectory is known, or can be reliably estimated on the basis of past experience, then the time to realise the limit-state event could be reliably estimated. In other words, the time of birth could be reliably predicted.

The embodiments described above could be presented as a computer program that is employed as an aid to clinicians in management of their patients. Normal and abnormal trajectories in each state-subspace could be displayed in different colours. This method could then be employed as a valuable predictor of abnormal pregnancy states. Normal and abnormal limit-state surfaces could also be displayed in different shadings. Multiple limit-state surfaces could be depicted in different colours, and highlighted by a 'light source' strategically located in relation to the observer. When multiple limit-state surfaces are depicted, only the 'closest' limit-state surfaces in relation to the current position may be displayed, thereby assisting visual clarity of the problem. Optimal or 'target' positions may be marked on a limit-state surface.

The time evolution of the trajectory and limit-state surfaces in the state-subspace could be animated to enhance understanding of the dynamic nature of the system. 'Zooming' and 'rotating' the computer image to position the viewer's vantage point at right-angles to the trajectory may facilitate comprehension of the situation. In other circumstances, rotating the viewer's vantage point to be at right angles in the limit-state surface at the anticipated interception point of the trajectory with the limit-state surface may be helpful in interpreting the results of the mathematical model (eg. viewing the marginal probability distributions).

Several state-subspaces may be viewed simultaneously

on a divided computer screen. Investigation of treatment alternatives by a clinician could be made by 'clicking' and 'dragging' the current position in a state-space to a new position in the state-space, this new position representing the effect of intervention. This 'virtual' intervention could then be assessed by computing updated positions of the limit-state surfaces in the multi-dimensional space. Graphically, this would be seen by the analyst as a limit-state surface 'swinging around' in the state-space. The clinician could be alerted to any intersections of trajectories and limit-state surfaces. The clinician could select the level of probability of realising a limit-state, and only those limit-states with a greater probability of occurrence would be brought to the attention of the clinician by a warning appearing on the screen.

It is often the case that limit-state surfaces are smooth, continuous, differentiable functions in the state-space. Further, it is often the case that a limit-state surface may be a finite 'patch' in the state-subspace (having a finite 'height' and 'length'), due to the range of biologically achievable values for the state variables being limited.

The state-space may have intersecting multi-dimensional limit-state surfaces. The intersection of limit-state surfaces is attributed to simultaneous satisfaction of several limit-states. For simultaneous realisation of several limit-states, the trajectory in the state-space must intersect the limit-state surfaces at one point see figure 5.

Processes that are sequential in time are represented by a set of limit-state surfaces that are intersected sequentially by the trajectory see figure 5.

Abnormalities of pregnancy can be made visually apparent from sequential intersection of limit-state surfaces rather than simultaneous intersection of the

limit-state surfaces. For example, if the 'cervical competence' limit-state surface is intersected before the 'uterine contractions' limit-state surface, then this indicates spontaneous abortion. On the other hand, intersection of the 'uterine contractions' limit-state surface before intersection of the 'cervical competence' limit-state surface can indicate rupture of the uterus.

More complex process controls, involving multiple process in series and parallel could also be presented geometrically in the state-space, this geometry being characteristic for the process. Further, as each disease has a characteristic set of clinical features, it is suggested that each disease process would have a 'characteristic geometry (or arrangement) of limit-state surfaces' in the chosen state-space, as well as 'characteristic trajectories' in the state-space.

Given this, it is possible to program into the model a vast library of disease state signatures, that is, sets of trajectories and arrangements of limit-state surfaces in defined state-spaces that are characteristic of particular disease states. Given suitable input, the library of disease states could be searched and the closest matches to the known trajectories of a patient being investigated displayed on a computer screen. Further, using statistical methods, the possible disease states for a given set of input data could not only be identified, but arranged in order of probability, from most likely to least likely disease. This could be a valuable clinical tool for the differential diagnosis of disease states.

It is conceivable that the data input to the computer may be at least partially automated. For example, biochemical data could be encoded in bar codes down the side of a laboratory report, while physiological data may be input from electronic monitoring devices. In addition, specific electronic systems may be built into the physical

structure of a hospital to facilitate the management of its patients using the method described herein.

Given that there could be a large number of limit-states for a particular disease process, it could be helpful to prioritise or group the limit-states surfaces in some way. For example, limit-state surfaces may be grouped in signs and symptoms of disease commonly employed by clinicians, while another group of limit-state surfaces may be more conveniently employed with biochemical data.

The invention may be easily adapted to include the influence of a drug on anticipated therapeutic outcomes. This influence may be reflected as a change in the shape of the limit-state surface and/or the position within the state-space. It is noted that given sufficient data, a data base of limit-state surfaces for subgroups within a population could be defined in a computer program. For example, women on a particular medication throughout their pregnancy.

In respect of other applications, the management of patients in intensive care could be an example application for the invention. Even after many years of training and practice, it is still very difficult to consider all likely implications when managing a critically ill patient. In this situation, it could be highly beneficial to 'test' a proposed intervention using the method of invention described here. It is easily imagined that the effect of administering a drug to a patient could be trialled on the computer, perhaps by the simple experiment of positioning the cursor on the current position in the state-space, 'clicking' at this position, and then 'dragging' the current position in the state-space to a new location. Even if only one or two subspaces were represented on the computer screen, the effect in `m' state-subspaces and on 'n' limit-state surfaces could be checked very quickly by calculation. If any limit-state surfaces were found to

intersect a trajectory in a state-subspace, the doctor could be alerted, perhaps by a message on the computer screen. The relevant state-subspace could then be viewed on the screen. This procedure can represent an enormous advance over simply trialling the drug in a patient as is presently the case, and perhaps realising too late that some unexpected event has occurred.

Example III: POORLY DEFINED SYSTEM BEHAVIOUR

Even when the system behaviour is very poorly defined, the invention may have some benefits. The state-variables may then be identified as 'risk factors', as they are commonly known. An example is provided by cardiovascular disease. Known risk factors, such as high blood pressure, overweight, family history of heart disease, smoking and high cholesterol may be taken as state variables. For this example, limit-states could be 'heart ischemia' or 'stroke'. The predictive power of the model may be poor, but this only reflects inadequate understanding of the underlying process, and indicates that additional factors are of significance. To further the example of cardiovascular disease, it has recently been established that homocysteine is an important risk factor. With this additional variable comprising the state-space, it is expected that the predictive power of the model would improve. It is evident from this simple example how the latest research data may be incorporated into a model in accordance with the invention, and so it can improve in its role as clinical tool as medical research advances.

Some disease states may be immediately incorporated in the embodiments described here, while others will require more research data. Examples of disease states that could immediately benefit from the approach described here include endocrine diseases, asthma, AIDS and the management of patients in intensive care.

Example IV: REPRESENTATION OF MULTI-DIMENSIONAL LIMIT STATE SURFACE

Rene Decartes represented a function in a 'cartesian plane'. This had simple visual appeal, and by this means, everyone clearly understood what was meant by the term 'function'. A function has one and only one value of the dependent variable 'y' associated with a value of the independent variable 'x'. This can be represented simply by means of a 'cartesian diagram', with 'x' plotted along the horizontal axis and 'y' plotted along the vertical axis.

It is not hard to generalise this result to two independent variables and one dependent variable. In this case, the variables 'x' and 'y' are the independent variables in the horizontal plane, and 'z' is the dependent variable in the vertical direction. In this case, the three dimensional 'cartesian' axes suffice to represent the two independent and one dependent variables. The outcome may be plotted as a two dimensional 'surface', the height above the 'xy' plane representing the magnitude of the dependent variable, or outcome. A line joining equal heights above the plane represent a 'level surface'.

Alternatively, each location in the 'xy' plane may be associated with a number, and a line drawn joining points in the 'xy' plane that are of equal magnitude. Such a map is known as a 'contour' map, and has the advantage of representing a three dimensional surface in only two dimensions (ie. the 'xy' plane). A limit-state surface may be represented by a contour on a contour map.

This is generalisable to four dimensions, the three axes representing the independent variables and the limit-state is represented as a 'level surface' in the three dimensional state-space.

Let there be a function describing a limit-state surface in n dimensional space, viz,

$$f = f\ (X,..,X_n)$$

It is then possible to hold all but three of the independent variables constant. The function is then reduced to four dimensions. These four dimensions are, the three cartesian axes (forming a state-subspace) and a value associated with each location in the state subspace (note that all the independent variables not in the state subspace are held constant). Now that the dimensionality is reduced, a level surface of function f can be conveniently depicted on a computer screen. Changes in the fourth dimension, i.e. resulting from changes in the values of the independent variables held constant for the representation, can be illustrated by replotting the function f in the three-dimensional state-subspace as altered by those changes. It is noted that more than one surface representing function f could be plotted within one graph to illustrate the dependency of the function f the variables in the state sub-space. This dependency of the function f on the state sub-space variables could be made visually apparent by colour shading in state sub-space or by textual features on the limit surface itself.

If there are twelve independent state variables, then the computer screen could be 'tiled' into four quadrants, and in each quadrant the procedure described in the previous paragraph adopted. That is, each 3-D state-subspace shown in each quadrant would represent the limit-state surface for all but three dependent variables held constant. If the limit-state surface involved the variables in each subspace, then the limit-state surface would be represented in that subspace. The trajectory of the state variables could be depicted in each state-subspace, together with the limit-state surface. Changes of the trajectory and/or the limit-state surface in one state-subspace could then be automatically "transformed" onto the other state-subspaces.

In some circumstances, the dimensionality of the

problem may be conveniently reduced by defining a new state variable, Y_k as a function of the state variables X_i, viz,

$$Y_k = h(X_1,\ldots,X_i,\ldots,X_1)$$

This procedure provides a means of systematically structuring medical information (for further details see Example V).

Using the terminology of `vector geometry', for complex systems, the `basis' vectors chosen for the n-dimensional state space may not be orthogonal, and that appropriate groupings of the variables may improve orthogonality of the chosen basis vectors. It is further noted that for poorly defined systems appropriate groupings of variables may be indicated by standard statistical techniques eg. factorial analysis. However, orthogonality of the basis vectors is not essential for the method described here to be implemented, given that the system is adequately characterised by research data.

Example V: SELECTION OF STATE-VARIABLES

A 'causation tree' 30 (see figure 6) can provide a systematic approach for the identification and arrangement of state-variables, thereby providing a means for structuring the system information.

Having chosen a dependent variable that is appropriate for the limit-state being investigated, a causation tree 30 may be constructed, showing all 'independent' state-variables 32, 33, 34 contributing to the value of the dependent variable 35. Each 'independent' state-variable may be viewed in turn as a dependent variable each with its own set of state-variables, e.g. 36, 37, 38. Hence each 'branch point', e.g. 40 is the starting point for another set of state-variables. This process may be geometrically represented as the 'causation tree' 30 (see Figure 6). It is noted that system complexity is qualitatively conveyed by the number of branches at each level. Further it is noted that interactions between variables is systematically

represented in the 'causation tree' by variables appearing more than once (hence state-variables may not be independent).

This structuring of information using a 'causation tree' provides a systematic means for identifying the state-variables employed in the mathematical model.

Well understood systems may be described in terms of the known variables. Poorly understood systems, or partly defined systems, may be defined in terms of new variables that represent groupings of variables. Established statistical methods are available for establishing the most appropriate variable groupings eg. factorial analysis.

The variables chosen for representation in the model described here may depend on the time scale over which the process evolves. For example, a 'glucose tolerance test' may evolve over a period of hours, while an investigation of diabetes may evolve over a period of years or decades. Different state-variables may be chosen for the analysis of the same system, depending on the time scale involved, thereby providing further means for systematically structuring system/medical information.

The previous paragraphs indicate that the state-variables chosen for an analysis are somewhat arbitrary, in that the state-variables employed must only lie further along the 'causation tree'. The actual variables chosen for measurement will therefore be dependent on many factors such as the state of knowledge, convenience of data collection, established medical practice, costs and other practical constraints associated with gathering data.

Example VI: APPLICABILITY TO 'NORMAL' STATES

The present invention may also be applied to monitor the evolution of a biological system towards a normal state. For example, the fitness level of an athlete training for a particular short term or long term goal

could be improved utilising the present invention. In that embodiment, the limit-state surface would define a predetermined fitness level within a multi-dimensional space. The variables of the multi-dimensional space could include resting heart rate, `stressed' heart rate, resting breathing rate, `stressed' breathing rate, isotonic and isometric muscle strength, haemoglobin concentration in the blood. The athlete's progress could then be monitored utilising a trajectory within the appropriate multi-dimensional space. The analysis and displaying of the trajectory and the limit-state surface could substantially be the same as described in the previous examples. In the particular example of the athlete preparing for a short or long term goal, previous trajectories of "successful" athletes during their preparation/training could be used to guide/evaluate the development of the athlete currently monitored.

The claims defining the invention are as follows

1. A method of analysing an evolution of a biological system comprising the steps of:

- determining a series of variables upon which a state of the biological system depend;
- mapping the variables to an n-dimensional space; and

wherein the evolution of the biological system is monitored utilising a trajectory formed from sets of the variables which define the states of the biological system at different times, thereby using time as a parameter in the n-dimensional space in a manner such that every point on the trajectory corresponds to at least one value of time.

2. A method as claimed in claim 1 further comprising the step of evaluating the evolution of the biological system utilising sets of predetermined values of the variables to formulate an n-dimensional surface representing a predetermined state of the biological system within the n-dimensional space.

3. A method as claimed in claim 2 wherein the step of evaluating the evolution of the biological system comprises predicting a progression of the trajectory.

4. A method as claimed in anyone of the preceding claims, wherein n is an integer greater than 2.

5. A method as claimed in claim 3, wherein the prediction of the progression of the trajectory is based on other trajectories determined in the n-dimensional space.

6. A method as claimed in claims 3 or 5, wherein the prediction of the progression of the trajectory is based on other trajectories determined in the n-dimensional space.

7. A method of representing a predetermined state of a biological system comprising the steps of:

- determining a series of variables upon which the predetermined state of the biological system depends;
- mapping the variables to an n-dimensional space;

and

- utilising sets of predetermined values of the variables to formulate an n-dimensional surface describing the predetermined state within the n-dimensional space.

8. A computer arranged to analyse an evolution of a biological system based on series of variables upon which a state of the biological system depends, the computer being arranged to:

- map the variables to an n-dimensional space; and
- monitor the evolution of the biological system based on a trajectory formed from sets of the variables which define the states of the biological system at different times.

9. A computer as claimed in claim 8, the computer further being arranged to evaluate the evolution of the biological system utilising sets of predetermined values of the variables to formulate an n-dimensional surface representing a predetermined state of the biological system within the n-dimensional space.

10. A computer as claimed in claim 9, wherein the evaluating comprises predicting a progression of the trajectory.

11. A computer as claimed in anyone of claims 8 to 10, wherein n is an integer greater than 2.

12. A computer as claimed in claim 10, wherein the computer is arranged to base the prediction of the progression of the trajectory on the previous development of the trajectory within the n-dimensional space.

13. A computer as claimed in claims 10 or 12, wherein the computer is arranged to predict the progression of the trajectory on the basis of other trajectories determined in the n-dimensional space.

14. A computer arranged to represent a predetermined state of a biological system based on a series of variables upon which the predetermined state of the biological system

depends, the computer being arranged to:

- map the variables to an n-dimensional space; and
- formulate an n-dimensional surface describing the predetermined state within the n-dimensional space, based on sets of predetermined values of the variables.

15. A computer readable storage medium comprising instructions to control a computer to analyse an evolution of a biological system based on series of variables upon which a state of the biological system depends, the instructions comprising instruction to control the computer to:

- map the variables to an n-dimensional space; and
- monitor the evolution of the biological system based on a trajectory formed from sets of the variables which define the states of the biological system at different times.

16. A computer readable storage medium as claimed in claim 15, wherein the instructions further comprise instructions to control the computer to evaluate the evolution of the biological system utilising sets of predetermined values of the variables to formulate an n-dimensional surface representing a predetermined state of the biological system within the n-dimensional space.

17. A computer readable storage medium as claimed in claim 16, wherein the evaluating comprises predicting a progression of the trajectory.

18. A computer readable storage medium as claimed in anyone of claims 15 or 17, wherein n is an integer greater than 2.

19. A computer readable storage medium as claimed in claim 17, wherein the instructions further comprise instructions to control the computer to base the prediction of the progression of the trajectory on the previous development of the trajectory within the n-dimensional space.

20. A computer readable storage medium as claimed in claims 17 or 19, wherein the instructions further comprise instructions to control the computer to predict the progression of the trajectory on the basis of other trajectories determined in the n-dimensional space.

21. A computer readable storage medium comprising instructions to control a computer to represent a predetermined state of a biological system based on a series of variables upon which the predetermined state of the biological system depends, the instructions comprising instructions to control the computer to:

- map the variables to an n-dimensional space; and
- formulate an n-dimensional surface describing the predetermined state within the n-dimensional space, based on sets of predetermined values of the variables.

FIG. 1

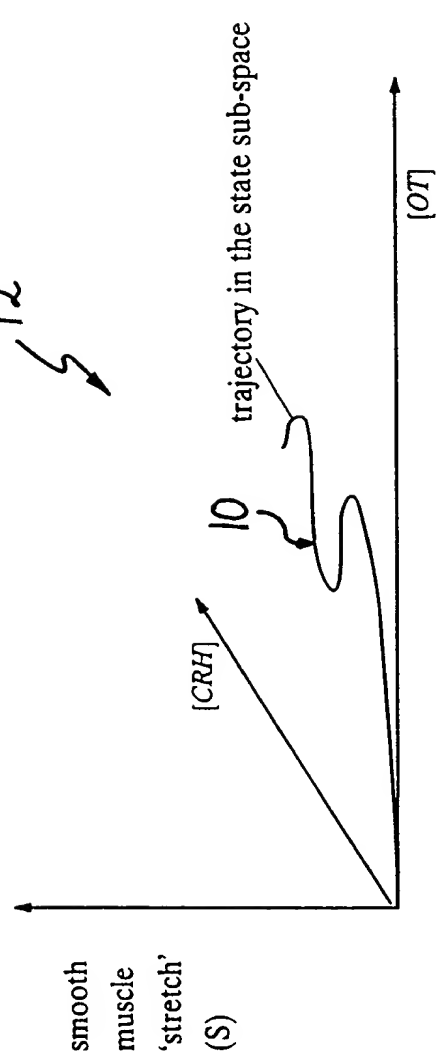

12
trajectory in the state sub-space
10
[CRH]
[OT]
smooth muscle 'stretch' (S)

FIG. 2

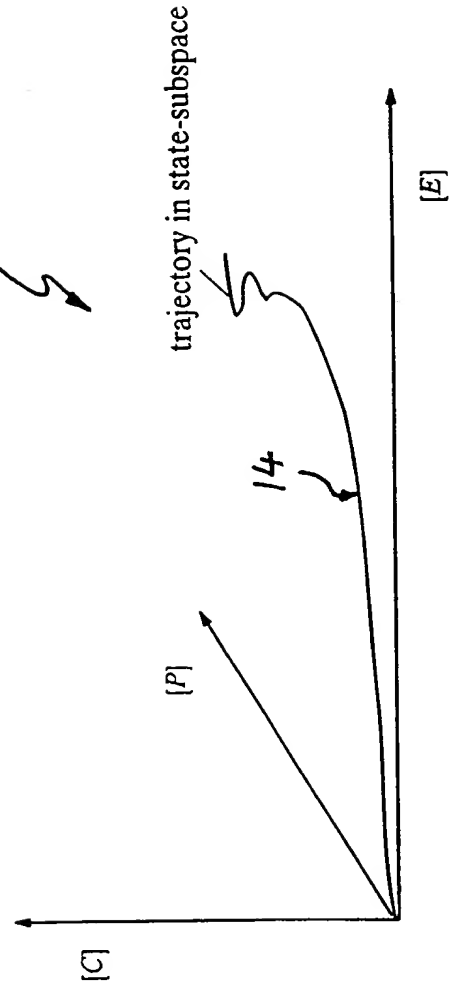

16
trajectory in state-subspace
14
[P]
[E]
[C]

FIG. 3

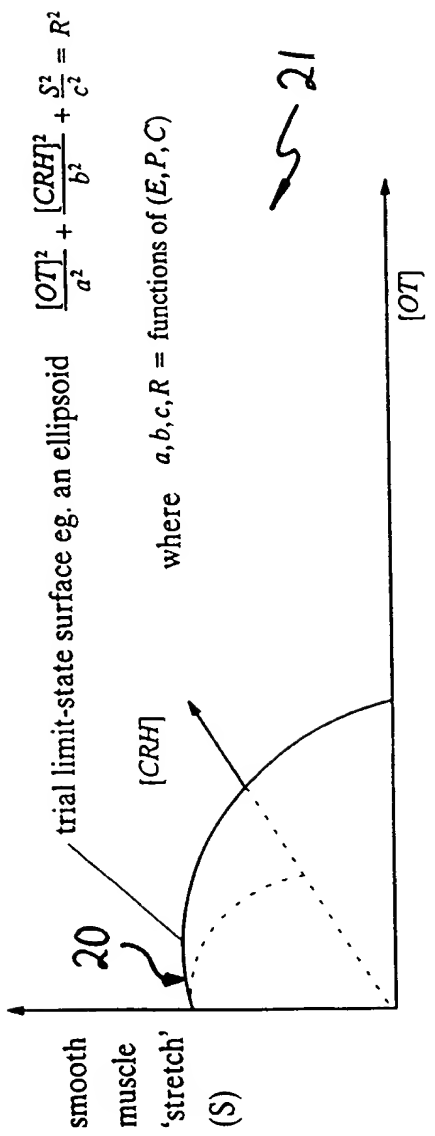
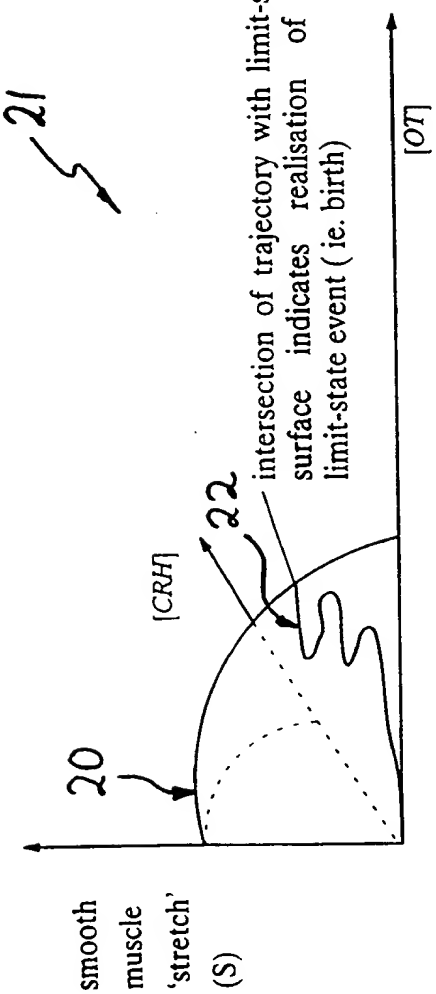

trial limit-state surface eg. an ellipsoid $\frac{[OT]^2}{a^2} + \frac{[CRH]^2}{b^2} + \frac{S^2}{c^2} = R^2$
where a, b, c, R = functions of (E, P, C)
21
20
[CRH]
[OT]
smooth muscle 'stretch' (S)

FIG. 4


21
22
intersection of trajectory with limit-state surface indicates realisation of the limit-state event (ie. birth)
20
[CRH]
[OT]
smooth muscle 'stretch' (S)

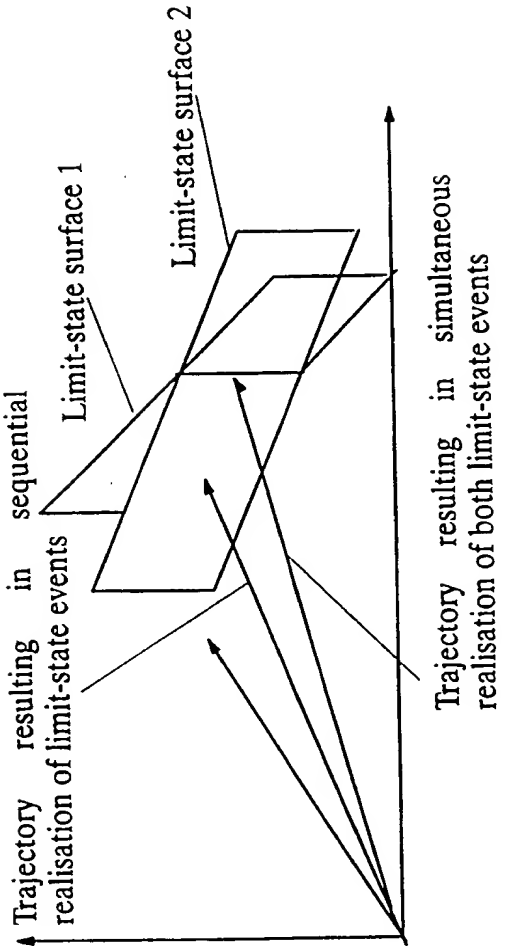

Limit-state surface 2
Limit-state surface 1
Trajectory resulting in sequential realisation of limit-state events
Trajectory resulting in simultaneous realisation of both limit-state events

FIG. 5

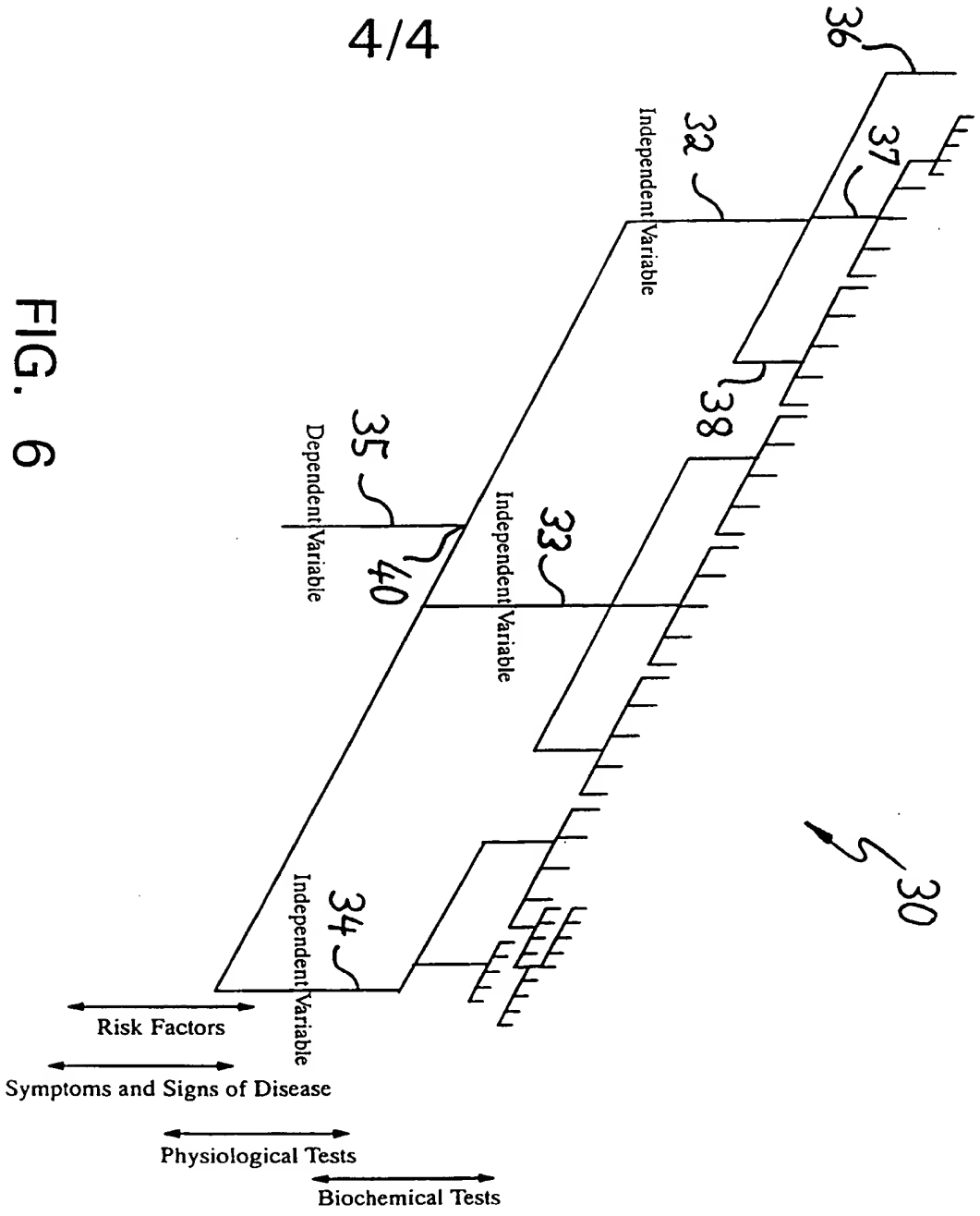

36
32
37
Independent Variable
38
35
Dependent Variable
40
33
Independent Variable
34
Independent Variable
30
Risk Factors
Symptoms and Signs of Disease
Physiological Tests
Biochemical Tests

FIG. 6